Study Title

COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

Laboratory Project ID:

Volume 13 of 13

NUMBER OF PAGES IN VOLUME: 196

TEST GUIDELINES:
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
- OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
- JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
- EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR:

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APPLICANT/SPONSOR:

PERFORMING LABORATORY:

WORK REQUEST NUMBER:

SERVICE CODE NUMBER:

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1612	S	**Microscopic**	
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- not examined
		pancreas	- within normal limits
		parathyroid glands	- hyperplasia, focal, bilateral, minimal
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1612	S	**Microscopic**	
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
1613	S	**Macroscopic**	
		adrenal glands	- enlarged, bilateral, mild
		kidneys	- focus/foci, tan, right, mild

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Macroscopic**	
		liver	- focus/foci, tan, caudate lobe, mild
			- mass, tan, mass c, median lobe, present
			approximately 2.0 cm in diameter.
		lymph node, hepatic	- within normal limits
			draining node for mass c.
		lymph node, inguinal	- not identified, bilateral, no grade
			draining node for mass a, left and mass b, right.
		skin, subcutis	- cyst, red, left anogenital region, moderate
			- mass, tan, mass a, left inguinal area, present
			corresponds to antemortem observation (mass 1)
			approximately 8.0 cm in diameter.
			- mass, tan, mass b, right inguinal area, present
			corresponds to antemortem observation (mass 2)
			approximately 5.5 cm in diameter.
1613	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
			corresponds to macroscopic observation (adrenal glands - enlarged)
			no medulla present

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		kidneys	- cyst, unilateral, moderate
			corresponds to macroscopic observation (kidneys - focus/foci, tan)
			- hydronephrosis, unilateral, mild
			- hyperplasia, transitional cell, unilateral, minimal
			- mineralization, pelvic, unilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		liver	- adenoma, hepatocellular, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (liver - mass c)
			- angiectasis, mild
			- focus of cellular alteration, basophilic, minimal
			- focus of cellular alteration, eosinophilic, mild
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, hepatic	- not examined
			misidentified tissue
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		mammary gland	- adenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - cyst)
			- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
			- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- dilatation, unilateral, mild

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1613	S	**Microscopic**	
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
		vagina	- within normal limits
		non-correlated macro observation	- liver - focus/foci, tan
1614	D	**Macroscopic**	
		cavity, thoracic	- fluid, red, moderate approximately 7.5 ml.
		kidneys	- irregular surface, bilateral, mild
		mediastinum	- enlarged, red, moderate red area continues along esophagus to thyroid glands.
1614	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1614	D	**Microscopic**	
		bone, sternum	- within normal limits
		brain	- within normal limits
		cavity, thoracic	- hemorrhage, severe
			corresponds to macroscopic observation (mediastinum - enlarged)
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, mild
			- edema, papilla, bilateral, mild
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
			corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1614	D	**Microscopic**	
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, eosinophilic, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1614	D	**Microscopic**	
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, minimal

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1614	D	**Microscopic**	
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- dosing injury
1615	D	**Macroscopic**	
		adrenal glands	- cyst, red, right, mild
		kidneys	- enlarged, bilateral, mild
		liver	- mass, tan, mass a, median lobe, present approximately 2.5 x 2.0 x 1.0 cm.
			- mass, tan, mass b, right lateral lobe, present approximately 0.9 x 0.6 x 0.6 cm.

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Macroscopic**	
		lung with bronchi	- focus/foci, tan, multiple lobes, mild
		lymph node, hepatic	- within normal limits
			draining node for mass a and mass b.
		mammary gland	- swollen/thickened, generalized, mild
			corresponds to antemortem observation (nodule)
			cervical region, anogenital, left and right inguinal areas most affected.
		pituitary gland	- enlarged, red, severe
		stomach, glandular	- swollen/thickened, mucosa, limiting ridge, mild
1615	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
			corresponds to macroscopic observation (adrenal glands - cyst)
			- hyperplasia, focal medullary, unilateral, mild
			- pheochromocytoma, malignant, unilateral, primary, incidental, not cause of death
		aorta	- within normal limits
		bone marrow, femur	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Microscopic**	
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- hyperplasia, focal, unilateral, mild
		heart	- cardiomyopathy, mild
		joint, tibiofemoral	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Microscopic**	
		kidneys	- dilatation, tubular, bilateral, mild
			- edema, papilla, bilateral, mild
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, pelvic, bilateral, mild
			- mineralization, tubular, bilateral, minimal
			- necrosis, papillary, unilateral, mild
			- nephropathy, chronic progressive, bilateral, moderate
			corresponds to macroscopic observation (kidneys - enlarged)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Microscopic**	
		liver	- adenoma, hepatocellular, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (liver - mass b)
			- carcinoma, hepatocellular, malignant, primary, incidental, not cause of death
			corresponds to macroscopic observation (liver - mass a)
			- focus of cellular alteration, basophilic, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- necrosis, focal, mild
			- vacuolation, periportal, minimal
		lung	- histiocytosis, alveolar, mild
			corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, hepatic	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
			corresponds to macroscopic observation (mammary gland - swollen/thickened)
		nerve, sciatic	- degeneration, axonal/myelin, minimal

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Microscopic**	
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1615	D	**Microscopic**	
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		non-correlated macro observation	- stomach, glandular - swollen/thickened
		Cause of Death	- pituitary tumor

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Macroscopic**	
		adrenal glands	- enlarged, left, minimal
		liver	- nodule, tan, median lobe, present approximately 0.4 cm in diameter.
		lymph node, iliac	- within normal limits draining node for mass b, bilateral.
		lymph node, mandibular	- within normal limits draining node for mass a, left.
		pituitary gland	- enlarged, tan, mild
		skin	- hair sparse, dorsal thoracic region, mild corresponds to antemortem observation (hair sparse)
		skin, subcutis	- mass, tan, mass a, left lateral neck, present corresponds to antemortem observation (swelling) approximately 4.0 x 3.0 x 1.5 cm.
		stomach, nonglandular	- swollen/thickened, limiting ridge, mild
		uterus with cervix	- mass, tan, mass b, body, present approximately 12.0 x 4.0 x 4.0 cm.
1616	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Microscopic**	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Microscopic**	
		kidneys	- dilatation, tubular, bilateral, minimal
			- edema, papilla, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, mild
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- adenoma, hepatocellular, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (liver - nodule)
			- hypertrophy, hepatocyte, centrilobular, minimal
			- necrosis, hepatocytes, centrilobular, moderate
		lung	- histiocytosis, alveolar, minimal
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Microscopic**	
		mammary gland	- fibroadenoma, benign, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Microscopic**	
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- mineralization, mild
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1616	D	**Microscopic**	
		uterus with cervix	- schwannoma, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (uterus with cervix - mass b)
		vagina	- within normal limits
		non-correlated macro observation	- stomach, nonglandular - swollen/thickened
		Cause of Death	- uterus tumor
1617	E	**Macroscopic**	
		adrenal glands	- cyst, clear, left, moderate cyst burst.
		lymph node, axillary	- discoloration, red, right, mild draining node for mass a.
		pituitary gland	- enlarged, red, severe
		skin, subcutis	- mass, tan, mass a, right axillary area, present corresponds to antemortem observation (swelling) approximately 5.0 x 3.5 x 2.0 cm.

E - Euthanized *in extremis*
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1617	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate
			corresponds to macroscopic observation (adrenal glands - cyst)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1617	E	**Microscopic**	
		kidneys	- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- necrosis, focal, minimal
		lung	- within normal limits
		lymph node, axillary	- erythrocytosis/erythrophagocytosis, sinus, mild
			corresponds to macroscopic observation (lymph node, axillary - discoloration, red)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1617	E	**Microscopic**	
		mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1617	E	**Microscopic**	
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1617	E	**Microscopic**	
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1618	S	**Macroscopic**	
		all tissues	- within normal limits
1618	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1618	S	**Microscopic**	
		eyes, retina	- within normal limits
			one of pair present
		galt	- within normal limits
		harderian glands	- hyperplasia, focal, unilateral, minimal
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, minimal
			- edema, papilla, bilateral, mild
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- degeneration, cystic, focal, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1618	S	**Microscopic**	
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1618	S	**Microscopic**	
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- not examined
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1619	E	**Macroscopic**	
		lymph node, axillary	- not identified, right, no grade draining node for mass a.
		lymph node, inguinal	- not identified, left, no grade draining node for mass b.
		skin, subcutis	- mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 6.0 x 6.0 x 2.5 cm.
			- mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 8.5 x 7.5 x 4.0 cm, tan.
		trachea	- fluid, clear, frothy, mild
1619	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1619	E	**Microscopic**	
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, eosinophilic, minimal
			- hematopoiesis, extramedullary, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1619	E	**Microscopic**	
		lung	- fibrosis, minimal
			- histiocytosis, alveolar, minimal
			- inflammation, acute, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death
		parathyroid glands	- not examined

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1619	E	**Microscopic**	
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1619	E	**Microscopic**	
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1620	E	**Macroscopic**	
		lymph node, iliac	- within normal limits draining node for mass a, bilateral.
		skin, subcutis	- mass, ulcerated, mass a, anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.0 cm in diameter, tan.
		uterus with cervix	- cyst, clear, body, moderate
			- enlarged, body, mild
1620	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1620	E	**Microscopic**	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		cavity, abdominal	- sarcoma, stromal, malignant, secondary corresponds to macroscopic observation (uterus with cervix - cyst) adjacent to uterus.
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1620	E	**Microscopic**	
		kidneys	- mineralization, pelvic, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- leukocytosis, sinusoidal, minimal
			- necrosis, focal, moderate
		lung	- histiocytosis, alveolar, minimal
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1620	E	**Microscopic**	
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1620	E	**Microscopic**	
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- hyperplasia, cervical fibromuscular, moderate
			corresponds to macroscopic observation (uterus with cervix - enlarged)
			- sarcoma, stromal, malignant, primary, fatal, positive cause of death
			corresponds to macroscopic observation (skin, subcutis - mass a)
		vagina	- hyperplasia, fibromuscular, moderate
		Cause of Death	- uterus tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1621	S	**Macroscopic**	
		liver	- mass, red, mass a, median lobe, present approximately 1.0 x 0.4 x 0.4 cm.
		lymph node, hepatic	- not identified, no grade draining node for mass a.
		pituitary gland	- cyst, red, mild
1621	S	**Microscopic**	
		adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1621	S	**Microscopic**	
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- adenoma, hepatocellular, benign, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass a)
			- degeneration, cystic, focal, minimal
			- focus of cellular alteration, basophilic, minimal
			- focus of cellular alteration, eosinophilic, minimal
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1621	S	**Microscopic**	
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - cyst)
		salivary gland, mandibular	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1621	S	**Microscopic**	
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1621	S	**Microscopic**	
		uterus with cervix	- within normal limits
		vagina	- within normal limits
1622	D	**Macroscopic**	
		liver	- focus/foci, tan, median lobe, left lateral lobe, mild
		lung with bronchi	- focus/foci, tan, multiple lobes, mild
		stomach, nonglandular	- swollen/thickened, limiting ridge, mild
1622	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
			- hyperplasia, focal cortical, unilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1622	D	**Microscopic**	
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
			- necrosis, papillary, bilateral, severe
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1622	D	**Microscopic**	
		liver	- adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death
			corresponds to macroscopic observation (liver - focus/foci, tan)
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, mild
			corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1622	D	**Microscopic**	
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- hyperplasia, focal, pars distalis, mild
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1622	D	**Microscopic**	
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		non-correlated macro observation	- stomach, nonglandular - swollen/thickened
		Cause of Death	- kidney inflammation/necrosis
1623	S	**Macroscopic**	
		adrenal glands	- enlarged, right, moderate
		lung with bronchi	- focus/foci, white, multiple lobes, mild
		lymph node, axillary	- within normal limits draining node for mass a, right.
		lymph node, inguinal	- within normal limits draining node for mass b, right.
		ovaries	- cyst, clear, left, mild
		pituitary gland	- enlarged, mild

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1623	S	**Macroscopic**	
		skin	- nodule, tan, dorsal lumbar region, present corresponds to antemortem observation (nodule) approximately 0.4 cm in diameter.
		skin, subcutis	- mass, tan, mass a, right axillary area, present approximately 2.2 x 1.5 x 1.0 cm.
			- mass, tan, mass b, right lateral abdomen, present approximately 1.2 cm in diameter.
		stomach, glandular	- swollen/thickened, moderate
1623	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- hyperplasia, granulocytic, minimal
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1623	S	**Microscopic**	
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- degeneration/atrophy, retina, unilateral, mild
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, basophilic, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1623	S	**Microscopic**	
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death
			corresponds to macroscopic observation (skin, subcutis - mass b)
			- fibroadenoma, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, moderate
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, mild
			corresponds to macroscopic observation (ovaries - cyst)
		oviducts	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1623	S	**Microscopic**	
		pancreas	- hyperplasia, acinar cell, focal, mild
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- keratoacanthoma, benign, primary, mortality-independent
			corresponds to macroscopic observation (skin - nodule)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1623	S	**Microscopic**	
		spleen	- within normal limits
		stomach, glandular	- leiomyoma, benign, primary, incidental, not cause of death
		stomach, nonglandular	- cyst, keratin, moderate corresponds to macroscopic observation (stomach, glandular - swollen/thickened)
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		non-correlated macro observation	- lung with bronchi - focus/foci, white
1624	E	**Macroscopic**	
		lymph node, axillary	- within normal limits draining node for mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1624	E	**Macroscopic**	
		lymph node, mandibular	- within normal limits draining node for mass a, right.
		pituitary gland	- enlarged, red, severe
		skin	- hair sparse, generalized, mild
		skin, subcutis	- mass, tan, mass a, cervical, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter, right.
			- mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 3.5 cm in diameter.
1624	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1624	E	**Microscopic**	
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, unilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1624	E	**Microscopic**	
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b)
			- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1624	E	**Microscopic**	
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- alopecia/hypotrichosis, moderate
			corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1624	E	**Microscopic**	
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, mild
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1625	D	**Macroscopic**	
		adipose tissue	- swollen/thickened, mild near hilus of liver. small, round, orange granules are on the surface.
		cavity, abdominal	- fluid, red, mild approximately 2.4 ml.

E - Euthanized *in extremis*
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1625	D	**Macroscopic**	
		lymph node, mandibular	- enlarged, red, mild
		skin	- hair sparse, left lateral neck, moderate
			corresponds to antemortem observation (hair sparse)
		spleen	- enlarged, moderate
1625	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bile duct, extrahepatic	- calculus/calculi, moderate
			bile stained.
			- dilatation, moderate
			corresponds to macroscopic observation (adipose tissue - swollen/thickened)
		bone marrow, femur	- bacterial colonies, mild
			- hyperplasia, granulocytic, mild
		bone marrow, sternum	- proliferation, fibro-osseous, moderate
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1625	D	**Microscopic**	
		brain	- bacterial colonies, minimal
			- inflammation, embolic, minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- bacterial colonies, mild
			- inflammation, moderate
			- thrombus, moderate left ventricle.
		joint, tibiofemoral	- within normal limits
		kidneys	- bacterial colonies, unilateral, minimal
			- edema, papilla, bilateral, minimal
			- inflammation, embolic, unilateral, minimal
			- mineralization, pelvic, unilateral, minimal
		lacrimal glands, exorbital	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1625	D	**Microscopic**	
		large intestine, cecum	- hypertrophy/hyperplasia, goblet cell, moderate
		large intestine, colon	- hypertrophy/hyperplasia, goblet cell, moderate
		large intestine, rectum	- hypertrophy/hyperplasia, goblet cell, moderate
		larynx	- within normal limits
		liver	- fibrosis, severe
			- inflammation, chronic-active, moderate
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- hyperplasia, lymphocyte/plasmacyte, medulla, mild
			corresponds to macroscopic observation (lymph node, mandibular - enlarged)
		lymph node, mediastinal	- hyperplasia, lymphocyte/plasmacyte, medulla, mild
			slide 14.
		lymph node, mesenteric	- hyperplasia, lymphocyte/plasmacyte, medulla, moderate
		mammary gland	- within normal limits
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1625	D	**Microscopic**	
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death slide 26-1.
			- bacterial colonies, severe within blood vessels.
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- cyst, mild
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- edema, mild
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- hypertrophy/hyperplasia, goblet cell, mild
		small intestine, ileum	- hypertrophy/hyperplasia, goblet cell, moderate

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1625	D	**Microscopic**	
		small intestine, jejunum	- hypertrophy/hyperplasia, goblet cell, moderate
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged)
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- erosion/ulcer, moderate
			- hyperplasia, squamous cell, mild
			- inflammation, subacute/chronic, mild
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- inflammation/septicemia

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Macroscopic**	
		liver	- focus/foci, tan, median lobe, mild
		lung with bronchi	- focus/foci, tan, multiple lobes, mild
		lymph node, axillary	- within normal limits draining node for mass a and mass b, right.
		lymph node, inguinal	- within normal limits draining node for mass c, right.
		ovaries	- cyst, clear, right, mild
		pituitary gland	- enlarged, moderate
		skin, subcutis	- mass, tan, mass b, right axillary area, present approximately 2.0 cm in diameter. - mass, tan, mass c, right anogenital region, present approximately 1.5 cm in diameter. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 2.0 x 1.2 cm, tan.
		stomach, glandular	- focus/foci, red, mucosa, mild
		stomach, nonglandular	- swollen/thickened, limiting ridge, mild
		thymus	- small, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
			- hyperplasia, focal medullary, unilateral, minimal
			- vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Microscopic**	
		kidneys	- edema, papilla, unilateral, minimal
			- hyperplasia, transitional cell, unilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- degeneration, cystic, focal, minimal
			- focus of cellular alteration, eosinophilic, moderate
			corresponds to macroscopic observation (liver - focus/foci, tan)
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, mild
			- infiltration, mononuclear cell, minimal
		lung	- histiocytosis, alveolar, mild
			corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, axillary	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Microscopic**	
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a)
			- fibroadenoma, benign, multiple, primary, incidental, not cause of death
			corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c)
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, minimal
			corresponds to macroscopic observation (ovaries - cyst)
		oviducts	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Microscopic**	
		pancreas	- atrophy, acinar, minimal
			- fibrosis, minimal
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1626	E	**Microscopic**	
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- erosion/ulcer, mild
			corresponds to macroscopic observation (stomach, glandular - focus/foci, red)
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, moderate
			corresponds to macroscopic observation (stomach, nonglandular - swollen/thickened)
		thymus	- depletion, lymphoid, generalized, severe
			corresponds to macroscopic observation (thymus - small)
		thyroid gland	- hyperplasia, c-cell, focal, unilateral, mild
		tongue	- hyperplasia, squamous cell, mild
			- inflammation, subacute/chronic, mild
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death
		vagina	- within normal limits
		Cause of Death	- mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1627	E	**Macroscopic**	
		lymph node, axillary	- within normal limits draining node for mass a, right.
		skin, subcutis	- mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1 scabbed area) approximately 3.0 cm in diameter, tan.
1627	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, minimal
		bone marrow, sternum	- hyperplasia, granulocytic, minimal
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1627	E	**Microscopic**	
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, mild
			- hydronephrosis, unilateral, mild
			- hyperplasia, transitional cell, unilateral, minimal
			- mineralization, pelvic, unilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hematopoiesis, extramedullary, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1627	E	**Microscopic**	
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1627	E	**Microscopic**	
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, minimal
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1627	E	**Microscopic**	
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1628	S	**Macroscopic**	
		uterus with cervix	- enlarged, horn, mild
1628	S	**Microscopic**	
		adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1628	S	**Microscopic**	
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, unilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, basophilic, mild
			- focus of cellular alteration, clear, minimal
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1628	S	**Microscopic**	
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- hyperplasia, sex-cord/stromal, bilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1628	S	**Microscopic**	
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - enlarged)
		vagina	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1629	D	**Macroscopic**	
		kidneys	- irregular surface, red, bilateral, mild
		lymph node, iliac	- within normal limits draining node for mass b, right.
		lymph node, inguinal	- within normal limits draining node for mass a, left.
		skin, subcutis	- mass, tan, mass a, left inguinal area, present approximately 1.0 x 1.0 x 0.5 cm.
		uterus with cervix	- mass, tan, mass b, horn, present approximately 4.0 x 3.0 x 1.5 cm.
1629	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1629	D	**Microscopic**	
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- edema, papilla, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- necrosis, papillary, bilateral, moderate
			- nephropathy, chronic progressive, bilateral, mild
			corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1629	D	**Microscopic**	
		liver	- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, iliac	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1629	D	**Microscopic**	
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1629	D	**Microscopic**	
		tongue	- hyperplasia, squamous cell, moderate
			- inflammation, subacute/chronic, mild
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - mass b)
		vagina	- within normal limits
		Cause of Death	- kidney inflammation/necrosis
1630	D	**Macroscopic**	
		lymph node, axillary	- within normal limits draining node for mass a, left.
		ovaries	- cyst, clear, right, mild
		pituitary gland	- enlarged, red, moderate

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1630	D	**Macroscopic**	
		skin, subcutis	- mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter.
		uterus with cervix	- cyst, clear, horn, mild
1630	D	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1630	D	**Microscopic**	
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- edema, papilla, bilateral, minimal
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
			- vacuolation, periportal, minimal
		lung	- histiocytosis, alveolar, mild
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1630	D	**Microscopic**	
		mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death slide 18.
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1630	D	**Microscopic**	
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		skin, subcutis	- fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1630	D	**Microscopic**	
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild
			corresponds to macroscopic observation (uterus with cervix - cyst)
		vagina	- within normal limits
		non-correlated macro observation	- ovaries - cyst
		Cause of Death	- pituitary tumor
1631	S	**Macroscopic**	
		all tissues	- within normal limits
1631	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1631	S	**Microscopic**	
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1631	S	**Microscopic**	
		liver	- focus of cellular alteration, basophilic, minimal
			- focus of cellular alteration, eosinophilic, minimal
			- hematopoiesis, extramedullary, minimal
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1631	S	**Microscopic**	
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
			- hyperplasia, epithelial cell, mild

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1631	S	**Microscopic**	
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death
		vagina	- within normal limits
1632	S	**Macroscopic**	
		skin	- hair sparse, left lateral neck, right lateral neck, mild corresponds to antemortem observation (hair sparse)
1632	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1632	S	**Microscopic**	
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- edema, papilla, bilateral, mild
			- hyperplasia, transitional cell, bilateral, mild
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1632	S	**Microscopic**	
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, minimal
			- hyperplasia, acinar cell, focal, mild
		parathyroid glands	- within normal limits
			one of pair present

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1632	S	**Microscopic**	
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1632	S	**Microscopic**	
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- hyperplasia, cervical fibromuscular, mild
		vagina	- within normal limits
1633	S	**Macroscopic**	
		lymph node, inguinal	- not identified, right, no grade draining node for mass a.
		pituitary gland	- enlarged, red, mild
		skin, subcutis	- mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 2.0 cm.
1633	S	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, mild - hyperplasia, focal cortical, unilateral, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1633	S	**Microscopic**	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1633	S	**Microscopic**	
		kidneys	- dilatation, tubular, bilateral, mild
			- edema, papilla, bilateral, mild
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- necrosis, papillary, bilateral, moderate
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- degeneration, axonal/myelin, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1633	S	**Microscopic**	
		nose, level a	- inflammation, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, minimal
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1633	S	**Microscopic**	
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
			- hyperplasia, epithelial cell, mild
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
			- hyperplasia, squamous cell, minimal
		vagina	- within normal limits

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1634	E	**Macroscopic**	
		lymph node, inguinal	- not identified, bilateral, no grade draining node for mass a, left and mass b, right.
		ovaries	- cyst, red, left, moderate
		pituitary gland	- enlarged, red, mild
		skin, subcutis	- mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 5.0 x 5.0 x 3.0 cm.
			- mass, ulcerated, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 3.5 cm in diameter, tan.
1634	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- hyperplasia, granulocytic, minimal
		bone, femur	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1634	E	**Microscopic**	
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- hyperplasia, transitional cell, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
			- pyelitis, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1634	E	**Microscopic**	
		liver	- hematopoiesis, extramedullary, minimal
			- hypertrophy, hepatocyte, centrilobular, mild
			- necrosis, focal, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b)
			- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
			- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- hemangiosarcoma, malignant, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (ovaries - cyst)
		oviducts	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1634	E	**Microscopic**	
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1634	E	**Microscopic**	
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1635	E	**Macroscopic**	
		lymph node, inguinal	- not identified, right, no grade draining node for mass a.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1635	E	**Macroscopic**	
		skin, subcutis	- mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 6.5 cm in diameter, tan.
1635	E	**Microscopic**	
		adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- hyperplasia, granulocytic, mild
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1635	E	**Microscopic**	
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, mild
			- edema, papilla, bilateral, minimal
			- hyperplasia, transitional cell, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hematopoiesis, extramedullary, minimal
			- hypertrophy, hepatocyte, centrilobular, mild
			- necrosis, hepatocytes, centrilobular, moderate
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1635	E	**Microscopic**	
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		skin, subcutis	- fibroma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		small intestine, duodenum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1635	E	**Microscopic**	
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- fibrosarcoma/fibroma

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Macroscopic**	
		liver	- focus/foci, tan, multifocal, multiple lobes, moderate
		lymph node, axillary	- within normal limits left is draining node for mass a. right is draining node for mass c.
		lymph node, iliac	- within normal limits right and left are draining nodes for mass e.
		lymph node, inguinal	- within normal limits left is draining node for mass b. right is draining node for mass d.
		pituitary gland	- enlarged, tan, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Macroscopic**	
		skin, subcutis	- mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 3.5 x 3.5 x 1.7 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (mass 3) approximately 4.8 x 3.7 x 1.8 cm. - mass, tan, mass d, right inguinal area, present corresponds to antemortem observation (swelling) approximately 1.8 x 1.0 x 0.6 cm. - mass, tan, mass e, anogenital region, present corresponds to antemortem observation (swelling) approximately 5.5 x 4.0 x 2.0 cm. - mass, ulcerated, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 x 3.5 x 2.0 cm and tan in color.
1636	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - hyperplasia, focal medullary, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Microscopic**	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- mineralization, tubular, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Microscopic**	
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hematopoiesis, extramedullary, minimal
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
			- necrosis, hepatocytes, centrilobular, moderate
			corresponds to macroscopic observation (liver - focus/foci, tan)
		lung	- adenocarcinoma, malignant, secondary
			- histiocytosis, alveolar, minimal
		lymph node, axillary	- within normal limits
		lymph node, iliac	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Microscopic**	
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass d)
			- fibroadenoma, benign, multiple, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass c; skin, subcutis - mass e)
			- hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Microscopic**	
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, moderate
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- not examined

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1636	E	**Microscopic**	
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
		vagina	- granular cell tumor, benign, primary, incidental, not cause of death
		Cause of Death	- mammary tumor
1637	E	**Macroscopic**	
		lymph node, axillary	- within normal limits draining node for mass e, right.
		lymph node, inguinal	- not identified, right, no grade draining node for mass a and mass b.
		lymph node, mandibular	- within normal limits draining node for mass c, right and mass d, left.
		pituitary gland	- enlarged, red, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Macroscopic**	
		skin, subcutis	- mass, red, mass d, ventral neck, left, present corresponds to antemortem observation (nodule) approximately 2.0 x 2.0 x 1.0 cm. - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 7.0 x 6.5 x 2.5 cm. - mass, tan, mass b, right anogenital region, present approximately 4.0 x 2.5 x 2.0 cm. - mass, tan, mass c, ventral neck, right, present corresponds to antemortem observation (nodule) approximately 3.0 x 2.5 x 1.0 cm. - mass, tan, mass e, right axillary area, present corresponds to antemortem observation (swelling) approximately 3.0 x 1.5 x 1.0 cm.
1637	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Microscopic**	
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, mild
			- mineralization, pelvic, bilateral, minimal
			- necrosis, papillary, bilateral, moderate
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Microscopic**	
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
			- necrosis, focal, minimal
			- vacuolation, median cleft, mild
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- not examined misidentified tissue
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Microscopic**	
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass d)
			- fibroadenoma, benign, multiple, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c; skin, subcutis - mass e)
			- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- foreign material, mild
			plant.
		nose, level d	- foreign material, mild
			plant.
		ovaries	- cyst, unilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Microscopic**	
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1637	E	**Microscopic**	
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1638	E	**Macroscopic**	
		kidneys	- focus/foci, white, left, mild
		lung with bronchi	- focus/foci, black, multiple lobes, moderate
		lymph node, iliac	- enlarged, left, mild draining node for mass a, bilateral.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1638	E	**Macroscopic**	
		skin, subcutis	- mass, ulcerated, mass a, anogenital region, bilateral, present corresponds to antemortem observation (mass 2 mass 1) approximately 12.2 x 6.5 x 4.5 cm, tan with some fluid present.
1638	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		bone, tibia	- proliferation, fibro-osseous, mild
		brain	- within normal limits
		cavity, abdominal	- adenocarcinoma, malignant, secondary corresponds to macroscopic observation (lymph node, iliac - enlarged)
		esophagus	- within normal limits
		eyes	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1638	E	**Microscopic**	
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- adenocarcinoma, malignant, unilateral, secondary corresponds to macroscopic observation (kidneys - focus/foci, white) from mammary tumor. - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1638	E	**Microscopic**	
		liver	- hematopoiesis, extramedullary, minimal
			- hyperplasia, bile duct, minimal
			- hypertrophy, hepatocyte, centrilobular, minimal
			- necrosis, focal, mild
			- necrosis, individual hepatocyte, mild
		lung	- adenocarcinoma, malignant, secondary
			corresponds to macroscopic observation (lung with bronchi - focus/foci, black)
			from mammary tumor.
			- hemorrhage, mild
			- macrophages, pigmented alveolar, mild
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1638	E	**Microscopic**	
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, bilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1638	E	**Microscopic**	
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, minimal
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
			- hyperplasia, follicular cell, unilateral, mild
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death
		vagina	- within normal limits
		Cause of Death	- mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1639	D	**Macroscopic**	
		all tissues	- within normal limits
1639	D	**Microscopic**	
		adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1639	D	**Microscopic**	
		kidneys	- cyst, unilateral, minimal
			- mineralization, tubular, unilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- within normal limits
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1639	D	**Microscopic**	
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1639	D	**Microscopic**	
		thymus	- within normal limits
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- dosing injury
1640	E	**Macroscopic**	
		adipose tissue	- focus/foci, yellow, mild white adipose tissue cranial to kidney on right side.
		pituitary gland	- enlarged, red, moderate
1640	E	**Microscopic**	
		adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits

E - Euthanized *in extremis*
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1640	E	**Microscopic**	
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, minimal
			- edema, papilla, unilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- necrosis, papillary, unilateral, severe
			- nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1640	E	**Microscopic**	
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
			- infiltration, mononuclear cell, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		mesentery/peritoneum	- necrosis, fat, mild
			corresponds to macroscopic observation (adipose tissue - focus/foci, yellow)
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1640	E	**Microscopic**	
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death
			corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
500 mg/kg/day			
1640	E	**Microscopic**	
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor

E - Euthanized *in extremis*

Appendix K
Section 2
Pathology Peer Review Statement

STUDY TITLE: Anatomic Pathology Peer Review Report for
Combined Chronic Toxicity/Oncogenicity Study
2-Year Oral Gavage Study in Rats

AUTHOR:

ANATOMIC PATHOLOGY PEER REVIEW REPORT COMPLETED: March 25, 2013

PERFORMING LABORATORY:

.

TESTING FACILITY:

LABORATORY PROJECT ID:

WORK REQUEST NUMBER:

SERVICE CODE NUMBER:

SPONSOR:

TESTING FACILITY STUDY NUMBER:

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The work performed at DuPont Haskell was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are compatible with current OECD Good Laboratory Practices.

Sponsor:

Principal Investigator: 25 March 2013
Date

Sponsor: _____
Date

QUALITY ASSURANCE STATEMENT

Number
Work Request Number:
Service Code Number:

Key inspections for the above referenced study's Peer Pathology Report were completed by the Quality Assurance Unit of and the findings were submitted on the following dates:

	Date Reported to:			
Audit Dates	***Principal Investigator (PI)***	***PI Management***	***Study Director (SD)***	***SD Management***
Report/Records:				
March 15, 17, 2013	March 18, 2013	March 18, 2013	March 18, 2013	March 19, 2013

Reported by: _ _ 25-MAR-2013
Date

CERTIFICATION

I, the undersigned, declare that these results provide accurate data obtained from this study.

Issued by
Principal Investigator: _____

25 March 2013
Date

SUMMARY

Gross observations, organ weights, microscopic findings, and the pathology report of this 2-year oral gavage study in rats with were peer reviewed according to the The peer review pathologist is in agreement with the conclusions of the study pathologist as given in the pathology report.

INTRODUCTION

This report documents the peer review of pathology data, including gross observations, organ weights, and microscopic findings for this study.

METHODS

A peer review of the gross observations, organ weights, microscopic findings, and the pathology report for was conducted for male and female Crl:CD(SD) rats by a peer review pathologist. The peer review was conducted at
and at

Twelve-Month Interim

For the twelve-month interim sacrifice, sections of all available tissues from the following animals in the male and female high-dose groups (Groups 4 and 5, respectively) were reviewed microscopically:

Males: 1241, 1245, and 1250

Females: 1561, 1565, and 1570

In addition, liver and testes from male rats; liver and kidneys from females rats; and all neoplasms in all male and female groups were examined microscopically.

Terminal (or 24-Month Terminal)

For the terminal sacrifice, sections of all available tissues from the following animals were reviewed microscopically:

Terminal Sacrifice		
Male Groups:	1	4
Animal Number(s):	1011	1256
	1029	1269
	1037	1275
	1050	1294
	1051	1298
	1057	1305
	1058	1316
Female Groups:	1	5
Animal Number(s):	1323	1591
	1336	1610
	1342	1619
	1358	1625
	1364	1628
	1384	1633
	1392	1634

In addition, liver, pancreas, and testes in males, and liver, kidneys, stomach, tongue, pancreas, and lungs in females were examined microscopically from all groups as potential target organs or to clarify findings in the high dose groups. All neoplasms in all two-year groups were also examined.

For both the 12-month interim and terminal sacrifice, other selected tissues were examined as necessary by the reviewing pathologist to clarify diagnostic terms and confirm microscopic findings. The pathology report and the summary incidence tables for gross findings, organ weight changes, and microscopic findings were also reviewed.

RESULTS

The quality of the histopathology sections and accountability of tissues for examination were good, and there was good agreement between the study pathologist and peer review pathologist regarding severity grading and diagnoses of lesions. Terminology and diagnoses were agreed upon by the study pathologist and the peer review pathologist for all the organs, and this agreement is reflected in the final report.

CONCLUSIONS

A peer review of the gross observations, organ weights, microscopic findings, and the pathology report for was conducted according to . The peer review pathologist is in agreement with the interpretations and conclusions of the study pathologist as given in the pathology report.

RECORDS AND SAMPLE STORAGE

For the work conducted at the anatomic pathology peer review report will be retained at

Appendix L
Computer Systems

Computer Systems

The computer systems used during the conduct of this study are presented in the following table.

Computer Systems	
Provantis™ v8.0:	Client-server, Oracle-based system used for electronic documentation and data management from compound receipt through reporting.
Siemens Environmental Monitoring vMPI1 and Niagara Framework® Software System v2.3:	Environmental monitoring, alarming, and reporting applications.
:	A comprehensive laboratory information management system used to manage data, including but not limited to: instrumentation, test articles, standards, and samples.
:	In-house developed application for automated storage and retrieval information for archiveable materials (e.g., lab books, study data, wet tissues, slides, etc.).
Enterprise Reporting System – Table Production System v1.14	In-house developed reporting system used primarily for reporting of Provantis™ data.
eDocs v3.3:	Electronic document management system.
Master Schedule v2.2:	Maintains the master schedule for the company.
MasterControl QAAD v8.0:	A quality management system, consisting of the QAAD and QAADLink applications, used to automate the Quality Assurance process for regulatory compliance.
SAS® v9.1:	The SAS® System is an integrated system of software products that enables a user to perform data entry, retrieval, data management, reporting, graphics, statistical analysis, and applications development.
docuBridge® v3.6/5.1:	Electronic publishing system.
Microsoft® Office Professional 2003/2010:	Suite of integrated productivity tools including word and data processing and communications software.

Additional information is available in the company document titled "Computer Systems Information."

Appendix M
Protocol and Amendments

Combined Chronic Toxicity/Oncogenicity Study
2-Year Oral Gavage Study in Rats

Work Request Number

Service Code

Protocol

July 8, 2010

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Study Number

Work Request/Study Code Number: D

1.2. Study Title

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

1.3. Sponsor

1.4. Sponsor Representative

1.5. Objective

The objective of this study is to evaluate the potential chronic toxicity and oncogenicity of when administered via oral gavage over the major portion of the life span of the test animals.

1.6. Regulatory Guideline

This protocol meets the United States Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Guideline 870.4300, Combined chronic toxicity/carcinogenicity, August 1998. The experimental design and methods are also based on the Organization for Economic Cooperation and Development (OECD) Guideline 453, September 2009, the Japanese Ministry of Agriculture, Forestry and Fisheries Guidelines for Data Requirements for Supporting Registration of Pesticides, No. 12-Nousan-8147, Notification by Director-General dated 24 November, 2000, and the Commission Directive 88/302/EEC B.33 Combined Chronic/Carcinogenicity test, *Methods for the Determination of Toxicity* (1988).

1.7. Good Laboratory Practice

This nonclinical laboratory study will be conducted in accordance with the United States Environmental Protection Agency FIFRA Good Laboratory Practice (GLP) Standards, 40 CFR Part 160, Toxic Substance Control Act Good Laboratory Practice Standards, 40 CFR Part 792, the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice ENV/MC/CHEM(98)17, and the Japanese Good Laboratory Practice Standards, 11 Nohsan No. 6283 and as changed in 12 Nohsan No. 8628, and 13 Seisan No. 1660.

1.8. Testing Facility

is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

1.9. Computer Systems

The following are the proposed computer systems to be used during the conduct of this study. The actual systems used will be documented in the final report.

Computer Systems	
Provantis™:	Client-server, Oracle-based system primarily used for toxicology studies.
Niagara Framework® Software System or Siemens Environmental Monitoring System (EMS):	Environmental monitoring, alarming, and reporting application.
Dispense:	Automates the test article control processes.
Microsoft® Windows XP:	Used in conjunction with Empower 2 software
Empower 2:	Empower 2 Chromatographic Data System used to quantitatively determine the amounts of analytes in samples, including test articles in formulation.
:	In-house developed application for automated storage and retrieval information for archiveable materials (e.g. lab books, study data, wet tissues, slides, etc.).
	In-house developed reporting system used primarily for reporting of Provantis™ data.
Master Schedule:	Maintains the master schedule for the company.

SAS®:	The SAS® System is an integrated system of software products that enables a user to perform data entry, retrieval, data management, reporting, graphics, statistical analysis, and applications development.
Microsoft® Office 2003 Professional:	Bundle of integrated productivity tools including word and data processing and communications software. Contains the utilities Microsoft® Access, Excel, InfoPath, Outlook, PowerPoint, Publisher, and Word.
docuBridge®:	Electronic publishing system.

1.10. Personnel

1.10.1. Study Director

1.10.2. Alternate Contact

1.11. Proposed Study Schedule

Study Initiation Date (EPA and OECD): (Date Study Director signs Study Approval-Initiation Line in the protocol)	Date Study Director signs Study Approval-Initiation Line in this protocol
Experimental Starting Date (OECD): (Date of the first data collection directly from the study)	July 15, 2010
Experimental Start Date (EPA): (Date of first test article exposure)	July 29, 2010
Experimental Termination Date (EPA): (Date of last animal termination)	August 3, 2012
Experimental Completion Date (OECD): (Date of the last data collection directly from the study)	Date Anatomic Pathology Contributor report is signed
Draft Report Mail Date:	To be added by amendment

1.12. Quality Assurance

This study will be subjected to periodic inspections and the data, draft and final reports will be reviewed by the Quality Assurance Department of in accordance with Standard Operating Procedures. Study quality assurance inspection records will be made available to the Sponsor Representatives during visits to

1.13. Alteration of Design

Alterations of this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, will honor such change. However, written authorization will be obtained thereafter. All protocol amendments and justifications will be documented, signed, and dated by the Study Director and Sponsor. The protocol and all amendments will be issued to the Sponsor as well as at

1.14. Declaration of Intent

This study may be submitted to an Organization for Economic Cooperation and Development (OECD) member country, the United States Environmental Protection Agency (EPA), and/or other country regulatory bodies.

2. TEST AND CONTROL ARTICLES

2.1. Description of Test Article

2.1.1. Identity

A description, lot number, storage conditions, expiration date, safe handling procedures, physical properties, as well as other relevant information will be documented in the study data.

2.1.2. Test Article Properties

The Sponsor will provide a certificate of analysis (COA) documentation on the purity, composition, stability, and other pertinent information, unless otherwise noted.

2.2. Test Article Preparation

The bulk test article will be stored at room temperature. The test article formulations will be adjusted for a purity of 84%. The test article will be mixed with deionized water to achieve the desired dose volumes. The vehicle and method of preparation will be determined based upon physical characteristics of the test article and size of batches required. Fresh formulations will be prepared for each concentration weekly and stored at room temperature when not in use.

2.3. Test Article Analysis

Test article formulations prepared for the study will be evaluated for homogeneity and concentration. Room temperature stability (at least 14 days) which covers the concentration range to be used in this study has been established in
No further stability analysis is necessary.

Appropriate samples (see table below) will be taken while the preparations are stirring. Homogeneity will be evaluated again if the batch size changes by more than 50% during the study or if a new concentration is outside of the range of concentrations previously evaluated. Following acceptance of the analytical results (signing of the final report) by the Study Director, or at the Study Director's discretion, backup samples will be discarded.

Analytical Sample Collection Table

Sample Type	Concen-trations to Sample	Stratum	Number of Samples per Concentration			Sample Volume (mL)	Intervals
			Collected	Analyzed	Back up		
Homogeneity Analyses[a]	All (except control)	Top Middle Bottom	6 6 6	2 2 2	4 4 4	1 1 1	Week 1
Concentration Analyses[a]	All (including control)	Middle	6	2	4	1	Weeks 1-4, every 3 months thereafter

[a]: *The samples will be stored frozen at approximately -20 °C pending analyses or final disposition.*

2.4. Analyses

All analytical work will be conducted by using an analytical method developed by and validated under The work performed in conjunction with this study will be conducted in compliance with GLPs and subject to review by the Quality Assurance Unit (QAU) of that laboratory. The findings of their QAU will be submitted to the Principal Investigator and the Principal Investigator's Management as well as to the Study Director and Management. A final report, including a Quality Assurance Statement, will be prepared and submitted to for inclusion as an appendix in the main study final report. Samples will be shipped on dry ice on Monday through Wednesday for next day delivery. The primary contact will be notified prior to each shipment.

Principal Investigator (Formulation Analyses)	Primary Contact for Sample Shipment

2.5. Reserve Sample

A reserve sample from each batch of test article used in this study will be collected and stored at in a secure area with the appropriate environmental controls. If multiple studies are conducted with the same test article, a common reserve sample may be taken and labeled appropriately.

2.6. Test Article Disposition

Any remaining test article will be returned to the Sponsor after completion of the study. The test article will be shipped to the following address:

will be notified prior to shipment.

2.7. Description of Vehicle

2.7.1. Identity

Deionized water

A description, lot number, storage conditions, expiration date, safe handling procedures, physical properties, as well as other relevant information will be documented in the study data.

2.7.2. Vehicle/Control Article Properties

The vehicle used will be from deionized tap water at the Testing Facility.

3. TEST SYSTEM

3.1. Species

Rat

3.2. Strain

CD® [Crl:CD(SD)]

3.3. Source

Charles River Laboratories

3.4. Justification of Test System

The current state of scientific knowledge and the applicable guidelines cited previously in this protocol do not provide acceptable alternatives, *in vitro* or otherwise, to the use of live animals to accomplish the purpose of this study. "The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species."[1] "Whole animals are essential in research and testing because they best reflect the dynamic interactions between the various cells, tissues, and organs comprising the human body."[2]

The rat is a frequently used model for evaluating the toxicity of various classes of chemicals and for which there is a large historical database.

3.5. Expected Age

The test animals will be approximately 4-5 weeks of age at arrival. All animals placed on study will be less than 8 weeks of age at the start of dosing.

3.6. Expected Body Weight

The males will weigh approximately 100 to 125 g and the females will weigh approximately 76 to 100 g at arrival, as measured within 3 days of arrival. The actual range may vary but will be documented in the data.

3.7. Number of Animals

3.7.1. Number Ordered

Males: 400
Females: 400

3.7.2. Number on Study (includes 25 sentinel animals per sex)

Males: 345
Females: 345

Females will be nulliparous and non-pregnant.

3.7.3. Justification for Number on Study

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards, and in consideration of applicable regulatory requirements cited previously in this protocol.

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[1] "Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training", Federal Register, 1985 May 20; 50(97).
[2] "Position Statement on the Use of Animals in Research", 1993 Feb 26; NIH Guide 22(8).

This study is designed to use the smallest number of animals possible that will allow sufficient group sizes for meaningful statistical analysis of data.

3.7.4. Selection for Study

All animals placed on study will have body weights that fall within ±20% of the mean body weight for each sex. If not enough animals fall within this weight range to satisfy the number of animals required to go on study, the Study Director will be notified to ascertain the appropriate action to be taken.

Animals considered suitable for study will be weighed prior to treatment. After the appropriate number of animals with the highest and lowest body weights has been excluded, the remaining required number of animals on study will be randomized, by sex, into treatment groups using a standard, by weight, measured value randomization procedure.

3.7.5. Method of Identification

Each animal will be assigned an animal number to be used in Provantis™ and will be implanted with a microchip bearing a unique identification number. The individual animal number, implant number, and the study number will comprise a unique identification for each animal. The animal cage will be identified by the study number, animal number, group number, and sex.

3.8. Husbandry

3.8.1. Acclimation

All animals will be permitted an acclimation period of approximately 2 weeks. During this acclimation period, all animals will be observed daily for any clinical signs of disease and all animals will be given a detailed clinical examination prior to selection for study. All animals with any evidence of disease or physical abnormalities will not be selected for study. The week prior to dose initiation, animals will be administered a sham dose of tap water on at least 2 occasions in the same manner and at the same volume intended for use during the study period.

3.8.2. Housing

The animals will be pair-housed (same sex) in solid-bottom cages (polyboxes). In order to foster the rat's natural chewing instinct and keep their teeth at a healthy length, approved chew toys (e.g. Nylabone) will be offered.

3.8.3. Environmental Conditions

Fluorescent lighting will be provided via an automatic timer for approximately 12 hours per day. On occasion, the dark cycle may be interrupted intermittently due to study-related activities. Temperature and humidity will be monitored and recorded daily and maintained to the maximum extent possible between 64 to 79° F and 30 to 70%, respectively.

3.8.4. Diet and Drinking Water

3.8.4.1. Basal Diet

The basal diet will be block Lab Diet® Certified Rodent Diet #5002, PMI Nutrition International, Inc. This diet will be available *ad libitum* unless designated otherwise. Each lot number used will be identified in the study records.

3.8.4.2. Basal Diet Contaminants

The Study Director is not aware of any potential contaminants likely to be present in the certified diet that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier will be conducted.

3.8.4.3. Water

Tap water will be supplied *ad libitum* via an automatic water system unless otherwise indicated.

3.8.4.4. Water Contaminants

The drinking water used will be monitored for specified contaminants at periodic intervals according to Standard Operating Procedures. The Study Director is not aware of any potential contaminants likely to be present in the water that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

3.9. Sentinel Animals

A health screen will be conducted pretest and at 6, 12, 18, and 24 months on 3-5 males and 3-5 females (depending on survival) using sentinel animals selected with a computerized randomization and euthanized via carbon dioxide inhalation for this purpose. If insufficient animals are available due to survival, fewer animals may be submitted for evaluation (Study Director consulted) and this will be noted in the final report. Approximately 1-2 mL of blood will be collected via the vena cava and serum obtained. Blood samples will be processed to serum and placed into 2 aliquots of approximate equal volume. Serum samples will be stored at approximately -20ºC. A gross necropsy will be performed at the time of blood collection. Gross lesions will be recorded. No tissues will be saved. Any sentinel animal that is found dead or euthanized *in extremis* will receive a gross necropsy and gross lesions will be saved for possible histopathologic evaluation.

The serum will be evaluated as indicated below:

3.9.1. Pretest and at months 12 and 24

- Pneumonia Virus
- Reovirus Type 3
- Theiler's Encephalomyelitis Virus (GD-7)
- Lymphocytic Choriomeningitis Virus

- Sendai Virus
- Mycoplasma Pulmonis
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus

3.9.2. At months 6 and 18

- Sendai Virus
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus
- Mycoplasma Pulmonis

Initial testing will be performed at For positive or inconclusive results, confirmation testing will be performed by Samples will be sent at ambient temperature to the following address, if necessary.

Any actions based on the results of the health screen will be determined after consultation with the Sponsor. Testing will not be conducted in accordance with GLPs. This will be included as a GLP exception in the final report. Results of these analyses will be maintained in the study file.

4. STUDY DESIGN

GROUP	Dose Level (mg/kg/day)	Number of Animals: Initial M	Initial F	Clinical Pathology[a] M	Clinical Pathology[a] F	12-Month Interim Necropsy[a, b] M	12-Month Interim Necropsy[a, b] F	Terminal Necropsy M	Terminal Necropsy F	Microscopic Pathology[c] M	Microscopic Pathology[c] F
1	0	80	80	10	10	10	10	70	70	80	80
2	0.1	80	-	10	-	10	-	70	-	AR	-
3	1	80	80	10	10	10	10	70	70	AR	AR
4	50	80	80	10	10	10	10	70	70	80	AR
5	500	-	80	-	10	-	10	-	70	-	80
89*	-	25	25	-	-	-	-	-	-	-	-

a: Hematology, and clinical chemistry will be performed on 10 animals/sex/group at 3 months. Hematology, coagulation, clinical chemistry, and urinalysis evaluations will be conducted on 10 animals/sex/group at 6 and 12 months. Differential blood smear will be prepared on all animals designated for necropsy at 12 months, all survivors at12, 18, and 24 months(termination), and all animals euthanized in extremis.
b: An interim necropsy will be conducted at 12 months on 10 animals/sex/group.
c: Animals from both the 12 month interim and terminal necropsies, and other animals as required..
AR = As Required: 1) Target tissues identified by high dose group evaluations, 2) Tissues in all animals found dead or euthanized in a moribund condition, and 3) gross lesions.
**Sentinel animals*

5. TEST AND CONTROL ARTICLE ADMINISTRATION

5.1. Route of Administration

The test and control articles will be administered by gavage.

5.2. Justification for Route of Administration and Dose Selection

The oral gavage route was selected as the most efficient way to administer an accurate dose.

In a previous study), Crl:CD(SD) rats (10/sex/dose) were dosed with the test substance by oral gavage for at least 90 days at daily doses of 0, 0.1, 10, or 100 mg/kg/day for males and 0, 10, 100, or 1000 mg/kg/day for females. In the 1000 mg/kg/day group, three females died prior to scheduled sacrifice and others displayed clinical signs. No other test substance-related effects were observed in surviving animals in all groups on body weight or nutritional parameters, clinical or ophthalmological observations, or neurobehavioral parameters.

Test substance-related findings included regenerative anemia (males: 100 mg/kg/day; females: 1000 mg/kg/day), clinical chemistry effects consistent with PPARα activation (males: ≥10 mg/kg/day; females: 100-1000 mg/kg/day), and increased liver weights and associated hepatocellular hypertrophy (males: ≥10 mg/kg/day; females: 1000 mg/kg/day). Similar liver effects were observed at ≥3 mg/kg/day in males and 300 mg/kg/day in females in a rat 28-day gavage study ( ). Increased kidney weights were observed in males and females at ≥10 mg/kg/day. In females, renal papillary necrosis and/or renal

tubular necrosis were observed in the two females found dead prior to scheduled sacrifice and in one female that survived to the scheduled sacrifice. Clinical and anatomic pathology parameters were fully or partially (male hematology effects; liver weights) reversible after an approximate 4-week recovery period.

Based on the results of the 90-day and 28-day studies, doses selected for this study were 0, 0.1, 1, and 50 mg/kg/day in males and 1, 50, and 500 mg/kg/day in females. The high dose is expected to produce effects on clinical chemistry and liver weight and microscopic pathology in males and females, without producing excessive liver toxicity. The middle dose may produce liver and clinical chemistry in either sex but could be a no-observed-adverse-effect level (NOAEL). The low dose is expected to be a NOAEL in both males and females.

5.3. Frequency and Duration of Administration

The test and control articles will be administered once per day, at approximately the same time of day (i.e., if the Day 1 dose occurs in the am, then subsequent doses should be delivered in the am for the study duration), for at least 104 weeks. The animals will be dosed up to the day prior to scheduled necropsy.

5.4. Dose Volume

10 mL/kg/dose

5.5. Test Article Administration

For administration, the test and control articles will be dosed via oral gavage in accordance with . The control animals will receive the control article at the same volume as the test article. Individual doses will be based on the most recent body weights.

6. ANTEMORTEM STUDY EVALUATIONS

6.1. Ophthalmoscopic Examinations

All animals in all groups will be examined prior to exposure and all surviving animals prior to the scheduled necropsy (interim and terminal) in accordance with . The ophthalmological examinations will be conducted by a veterinary ophthalmologist.

6.2. Cageside Observations

All animals will be observed at least twice a day for morbidity, mortality, injury, and availability of food and water in accordance with The afternoon cageside observation will be conducted at the same approximate time of day (± 2 hours). Beginning on Week 53, a third mortality check in the evening will also be conducted. Any animals in poor health will be identified for further monitoring and possible euthanasia.

Any abnormal findings noted in the morning cageside observation will be recorded by exception (i.e., ‘no abnormalities detected’ will not be captured on a daily basis for every animal).

6.3. Detailed Clinical Examinations

A detailed clinical examination of each animal will be performed once during each study week in accordance with . Observations will include, but will not be limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, bizarre behavior, and palpation of tissue masses in accordance with

6.4. Body Weights

Body weights will be measured and recorded within 3 days of arrival, at least once prior to randomization, weekly during the first 13 weeks starting on Day 1 (prior to dosing), and every other week thereafter in accordance with The individual and mean group mean body weights gain will be calculated and reported weekly (starting on Week -1), for the first quarter (Weeks 1-13), the first year (Weeks 1-52), and the entire study (Weeks 1-104).

6.5. Food Consumption

Food consumption will be measured and recorded pretest (Week -1), weekly during the first 13 weeks, and for 2 weeks intervals starting at Week 14 (i.e., food consumption will represent a 14 day interval) in accordance with . Food consumption will be measured for the cage and divided by the number of surviving animals. The individual and mean group mean food consumption and food efficiency will be calculated and reported weekly (starting on Week -1), for the first quarter (Weeks 1-13), the first year (Weeks 1-52), and the entire study (Weeks 1-104).

6.6. Clinical Pathology

The animals will have free access to drinking water but will be fasted overnight (no more than 16 hours) prior to sample collection. Blood samples (approximately 3 mL) taken at non-terminal intervals will be taken via the sublingual vein. Blood samples (3-5 mL) taken at necropsy will be taken via the vena cava. Blood samples (0.5 mL) for blood smears taken from animals not scheduled for full clinical pathology evaluation or euthanized *in extremis*, where possible, will be taken via the sublingual vein. Where possible, the animals designated for clinical pathology evaluations at 3 and 6 months will be the same animals evaluated at 12 months.

The order of bleeding and analysis will be alternating (one animal from each dose group, then repeating) to reduce handling and time biases. If samples need to be recollected for hematology, coagulation, or urinalysis for sample quality purposes (e.g., clotted sample), animals do not need to be fasted.

The following clinical pathology tests will be conducted.

6.6.1. Hematology

6.6.1.1. Number of Animals

10/sex/group at 3, 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.1.2. Collection Intervals

3, 6, and 12 months

6.6.1.3. Parameters Evaluated

- leukocyte count (total and absolute differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)
- absolute reticulocytes
- platelet count
- blood cell morphology

6.6.2. Coagulation

6.6.2.1. Number of Animals

10/sex/group at 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.2.2. Collection Intervals

6 and 12 months

6.6.2.3. Parameters Evaluated

- prothrombin time
- activated partial thromboplastin time

6.6.3. Clinical Chemistry

6.6.3.1. Number of Animals

10/sex/group at 3, 6, and 12 months (Animals designated for chronic toxicity evaluation)

6.6.3.2. Collection Intervals

3, 6, and 12 months

6.6.3.3. Parameters Evaluated

- alanine aminotransferase
- alkaline phosphatase
- sorbitol dehydrogenase
- total protein

- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- urea nitrogen
- creatinine
- total cholesterol
- triglycerides
- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dl)
- aspartate aminotransferase
- total bile acids
- glucose
- calcium
- phosphorus
- electrolytes (sodium, potassium, and chloride
- gamma glutamyl transferase

6.6.4. Urinalysis

Animals will be placed in stainless steel metabolism cages for at least 12 hours to collect urine.

6.6.4.1. Number of Animals

10/sex/group at 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.4.2. Collection Intervals

6 and 12 months

6.6.4.3. Parameters Evaluated

- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- blood
- urobilinogen
- microscopy of centrifuged sediment

6.6.5. Peripheral Blood Smears

6.6.5.1. Number of Animals

All surviving animals (animals designated for carcinogenicity evaluation) and just prior to necropsy for animals euthanized *in extremis*

6.6.5.2. Collection Intervals

12 and 18 months and prior to termination (24 months)

Peripheral blood smears will be prepared and held for possible future analysis from all surviving animals at 12, 18, and 24 months (study termination). The total and differential leukocyte count will be made on those animals in the control and highest dose group (Groups 1 and 4 or 5) at termination. If these data, or data from the pathology examination, indicate a need, then the blood smears from the other dose groups and/or earlier time point will also be examined. If clinical observations suggest a deterioration of health of the animals during the study, a differential blood count of the affected animals will be performed.

7. EUTHANASIA

7.1. Moribundity

Any moribund animals, as defined by a Testing Facility Standard Operating Procedure), will be euthanized for humane reasons and to prevent the loss of tissues through autolysis. All animals euthanized *in extremis* or found dead will be subjected to a routine necropsy. Where practical, a full set of tissues as listed in the Postmortem Study Evaluations portion of this protocol will be collected and preserved in the appropriate fixative.

7.2. Method of Euthanasia

Euthanasia will be by carbon dioxide inhalation followed by a SOP) approved method to ensure death, e.g. exsanguination.

7.3. Final Disposition

All surviving animals placed on study will be euthanized at their scheduled necropsy or, if necessary, euthanized *in extremis*. Extra animals obtained for this study, but not placed on study, will be transferred to either an stock or training colony, or euthanized and discarded. The final disposition of each animal will be documented in the study records.

8. POSTMORTEM STUDY EVALUATIONS

Complete necropsy examinations will be performed under procedures approved by a veterinary pathologist on all animals dying spontaneously, euthanized *in extremis*, or euthanized at scheduled necropsies in accordance with Examinations will be performed 7 days a week. Animals that are found dead after regular working hours will be refrigerated overnight and necropsies performed at the start of the next working day. At the appropriate intervals (after 12 and 24 months), all appropriate animals will be euthanized and examined.

The animals will be examined carefully for external abnormalities including palpable masses. The skin will be reflected from a ventral midline incision, and any subcutaneous masses will be identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities will be examined for abnormalities and the organs removed, examined, and, where

required, placed in fixative. The pituitary will be fixed *in situ*. The eyes and testes will be fixed using a modified Davidson's fixative[3]. All other tissues will be fixed in neutral buffered formalin. Formalin will be infused into the lung via the trachea and into the urinary bladder.

Body weight and the organ weights identified in the following table will be recorded for all animals at scheduled necropsies and appropriate organ weight ratios will be calculated (relative to body and brain weights). Paired organs will be weighed together. A combined weight of the thyroid gland with the bilateral parathyroid post fixation will be obtained. Organs will not be weighed for animals dying spontaneously or euthanized *in extremis*.

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections will be performed on sections of tissues and from the groups identified in the following table and all animals dying spontaneously or euthanized *in extremis*.

Organs or Tissues to be Weighed, Preserved, and Microscopically Examined

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) [a]	
			1, 4/5	2-3/4
Adrenal gland	X	X	X	
Aorta		X	X	
Bone with bone marrow, femur		X	X	
Bone with bone marrow, sternum		X	X	
Bone marrow smear[b]		X		
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X	X	
Coagulating gland		X	X	
Epididymis	X	X	X	
Esophagus		X	X	
Eye (with retina and optic nerve)		X	X	
GALT[c]		X	X	
Harderian gland		X	X	

[3] Latendresse JR, Warbrittion AR, Jonassen H, Creasy DM. Fixation of testes and eyes using a modified Davidson's fluid: comparison with Bouin's fluid and conventional Davidson's fluid. Toxicol Pathol. 2002 Jul-Aug;30(4):524-33.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) [a]	
			1, 4/5	2-3/4
Heart	X	X	X	
Joint, tibiofemoral		X	X	
Kidney	X	X	X	
Lacrimal gland, exorbital		X	X	
Large intestine, cecum		X	X	
Large intestine, colon		X	X	
Large intestine, rectum		X	X	
Larynx		X	X	
Liver	X	X	X	
Lung with bronchi		X	X	
Lymph node, mandibular		X	X	
Lymph node, mesenteric		X	X	
Mammary gland (process females only)		X	X	
Nerve, sciatic		X	X	
Nose (4 sections)		X	X	
Ovary with oviduct	X	X	X	
Pancreas		X	X	
Pharynx		X	X	
Pituitary		X	X	
Prostate		X	X	
Salivary gland, mandibular		X	X	
Salivary gland, parotid		X	X	
Salivary gland, sublingual		X	X	
Seminal vesicles		X	X	
Skeletal muscle, biceps femoris		X	X	
Skin		X	X	
Small intestine, duodenum		X	X	
Small intestine, ileum		X	X	

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) [a]	
			1, 4/5	2-3/4
Small intestine, jejunum		X	X	
Spinal cord, cervical		X	X	
Spinal cord, lumbar		X	X	
Spinal cord, thoracic		X	X	
Spleen	X	X	X	
Stomach, glandular		X	X	
Stomach, nonglandular		X	X	
Target Organs[d]		X	X	X
Testis	X	X	X	
Thymus		X	X	
Thyroid gland (with parathyroid)[e]	X	X	X	
Tongue		X	X	
Trachea		X	X	
Ureters		X	X	
Urinary bladder		X	X	
Uterus with cervix	X	X	X	
Vagina		X	X	
Gross lesions		X	X	X
Tissue masses with regional lymph node[f]		X	X	X

[a] *Microscopic examination will be conducted in controls and in Group 4 males and Group 5 females, the respective high dose for each sex.*
[b] *Bone marrow smears will be prepared only for animals necropsied at scheduled intervals. Evaluation will be performed at the discretion of the Study Director and/or Sponsor (additional cost).*
[c] *Gut associated lymphoid tissue*
[d] *Target organs (and target organ gross lesions) will be designated by the Study Director, Pathologist and/or Sponsor based on experimental findings (additional cost).*
[e] *Parathyroids cannot always be identified macroscopically. They will be examined if in the plane of section and in all cases where they are noted as grossly enlarged.*
[f] *A regional lymph node drains the region where a tissue mass is located.*

The presence of test article-related lesions in animals from the high dose group will require microscopic examination of the affected target tissue(s) in all animals from the lower dose groups. If mortality in the high dose groups is sufficiently high to preclude assessment of a potential toxic response, all protocol-required tissues from all animals in the next lower dose group will be examined after consultation with the Sponsor (additional cost).

The pathologist may use special stains and techniques as needed to aid in the diagnosis of specific lesions. If after routine sectioning, a tissue is missed, the block will be resectioned once or the tissue re-embedded for resectioning. If the tissue is still missing, the block will not be resectioned unless the missing tissue is determined to be a target organ. In this case, the tissue will be resectioned until located or until it is determined that it is not present in the block or in wet tissue. All missing tissues will be identified in the pathology portion of the final report. Tissues that are unintentionally sectioned or present in the plane with a required tissue, though not required by protocol, will be examined and documented, if abnormal.

A pathologist other than the study pathologist will perform a formal peer review of the histopathologic findings. This review will consist of an examination of all tissues determined to be target organs by the study pathologist, all neoplasms diagnosed in the study and all tissues from 10% of the animals selected randomly from control and high dose groups. Other selected tissues may be examined at the discretion of the reviewing pathologist. A signed statement by the reviewing pathologist will appear in the final report.

9. STATISTICS

The following is the proposed analysis plan to be used when data assumptions are met. If there are deviations to this plan due to violations of assumptions or if any other techniques are used (Sponsor consulted), they will be documented in the final report.

Table of Statistical Comparisons

Control Group	Treatment Groups
1	2, 3, 4, 5

The above table defines the set(s) of comparisons to be used in the statistical analyses described below. If more than one set of comparisons is required, all analyses will be conducted separately on each set unless stated otherwise. Data for each sex within a set will also be analyzed separately.

The raw data will be tabulated within each time interval, and the mean and standard deviation will be presented for each endpoint by sex and group. For each endpoint, treatment groups will be compared to the control group using the analysis outlined below. Data for some endpoints, as indicated, will be transformed by either a log or rank transformation prior to conducting the specified analysis.

Endpoints	Type of Analysis
Body Weight Body Weight Gain Food Consumption Hematology (except Leukocyte Counts) Coagulation Clinical Chemistry Organ Weights Absolute Weights Relative to Body and Brain Weight	Group Pair-wise Comparisons
Leukocyte Counts Total Leukocyte Counts Differential Leukocyte Counts	Log Transformation Group Pair-wise Comparisons (Levene's/ANOVA-Dunnet's/Welch's)
Urinalysis Urine Volume Specific Gravity pH	Rank Transformation with Dunnett's Test
Mortality Data	Survival Analysis
Tumor Data	Tumor Analysis
Non-Tumor Microscopic Pathology Data	To be determined if required

9.1. Group Pair-Wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)

If sample sizes for all groups are 3 or greater, Levene's test[4] will be used to assess homogeneity of group variances for each specified endpoint (see table above) and for all collection intervals. If Levene's test is not significant ($p \geq 0.01$), a pooled estimate of the variance (Mean Square Error or MSE) will be computed from a one-way analysis of variance (ANOVA) and utilized by a Dunnett's[5] comparison of each treatment group with the control group. If Levene's test is significant ($p < 0.01$), comparisons with the control group will be made using Welch's t-test[6] with a Bonferroni correction.

In the case that sample size is less than 3 for at least one treatment group, Levene's method cannot be implemented. Groups with sample sizes less than 3 will be excluded from the analysis and control-treatment pair-wise comparisons that satisfy the sample size assumption ($n \geq 3$) will be conducted using Welch's t-test with a Bonferroni correction.

[4] Milliken GA, Johnson DE. Analysis of messy data. London: Chapman and Hall: 1992.
[5] Dunnett, CW. A multiple comparison procedure for comparing several treatments with a control. J Am Stat Assoc 1955;50:1096-1121.
[6] Welch BL. The significance of difference between two means when the population variances are unequal. Biometrika 1937;29:350-362.

If there are only 2 groups involved, the above methodology applies and the Dunnett's test reduces to a Student's t-test[7].

Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

9.2. Log Transformation with Group Pair-wise Comparisons

Historical data indicates that leukocyte counts (total and differential) are not normally distributed; therefore, a log transformation will be performed on these data. The transformed data will then be analyzed as described in the Group Pair-wise Comparisons section.

9.3. Rank Transformation with Dunnett's Test

Historical data indicate that this endpoint has unpredictable distribution characteristics, thus analysis would be enhanced by use of a non-parametric test. For each specified endpoint (see table above) and for each collection interval, a rank transformation will be performed. The transformed data will then be analyzed using Dunnett's test, to compare each treatment group with the control group.

If sample size for the control group is 2 or greater, Dunnett's test will be used to compare each treatment group having a non-zero sample size with the control group.

If there are only 2 groups involved, the above methodology applies and the Dunnett's test reduces to a Student's t-test[7]. Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

9.4. Survival Analysis

Intercurrent mortality data will be analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups will be conducted using a log-rank test[8]. If this overall test is significant ($p<0.05$) and there are more than two groups, then a follow up analysis will be done where each treatment group will be compared to the control group using a log-rank test.

Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests.

9.5. Tumor Analysis

Tumor incidence data will be analyzed using both survival adjusted and unadjusted tests. The unadjusted tests will be based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test[9] will be calculated and Fisher's exact test[10]

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[7] Steel RGD, Torrie JH. Principles and Procedures of Statistics. A biometrical approach. New York: McGraw-Hill; 1980.
[8] Allison PD. Survival analysis using the SAS system: A Practical Guide. Cary (NC). SAS Institute Inc.; 1995.
[9] Agresti A. Categorical data analysis. 2nd ed. New York: John Wiley and Sons; 2002.

will be used to compare each treatment group with the control group. The survival adjusted test will be conducted according to the prevalence/mortality methods described by Peto et al.[11]. Evaluation criteria (p-values of significance) will be applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%)[12]. The evaluation criteria are given in the following table.

Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Electronic data will be provided for this study with the final report. The format of the data sets will be prepared following the guidelines of the United States Environmental Protection Agency (EPA).

10. STUDY REPORTS

10.1. Progress/Status Reports

Regular progress reports will be submitted to the Sponsor weekly for the first 5 weeks and biweekly reports through the first quarter (Week 13). Thereafter, progress reports will be sent approximately once per month.

10.2. Final Report

After completion of the study, a comprehensive draft report containing the results of all tests, analyses, observations and measurements required by this protocol, and an interpretative summary of the study results will be submitted to the Sponsor. The report will include all items required by the applicable regulatory agency. After receipt of any Sponsor comments, 1 copy (unbound) of the final report will be issued. An electronic copy (PDF) will be provided with the final report. This electronic copy will be searchable, hyperlinked (including headings, tables, figures, references, and all tables of contents), and bookmarked. One electronic copy will be in Microsoft Word, where possible. The electronic copies can be sent on CDs.

Six months after issuance of the draft report, if no requested revisions or instructions to finalize have been communicated by the Sponsor, the draft report will be issued as a final

[10] Zar JH. Biostatistical Analysis. 4th ed. New Jersey: Prentice Hall; 1999.
[11] Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Pete J, Richards S, Wahrendorf J. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal. Annex to Supplement 2. p. 311-426. International Agency for Research on Cancer, Lyon; 1980.
[12] Haseman JK. A reexamination of false-positive rates for carcinogenesis studies. Fund Appl Toxicol 1983;3:334-339.

report, signed by the Study Director, and submitted to the Sponsor. Any modifications or changes to the draft report requested 6 months after issuance of the draft will be performed at additional cost to the Sponsor.

11. DATA AND SPECIMEN RETENTION

All raw data, documentation, records, protocol, specimens, samples and the final report generated as a result of this study will be retained at or an contracted archive facility for a period of 1 year following the issuance of the draft report. The Sponsor will be contacted annually by Archive staff regarding the retained material and will be responsible for the incurred costs for the return, disposal, or continued storage of any study generated material retained after that time.

12. ANIMAL WELFARE

is committed to complying with all applicable regulations governing the care and use of laboratory animals. Animal welfare for this study will be in compliance with the U.S. Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2 and 3). The Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Academy Press, Washington, D.C., 1996, will be followed. This facility maintains an Animal Welfare Assurance statement with National Institutes of Health, Office of Laboratory Animal Welfare.

To ensure compliance:

A. This protocol will be reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) before animal receipt or transfer.

B. The Sponsor, by his or her approval, attests that the activities specified in this protocol do not unnecessarily duplicate any previous experiment.

C. The Study Director has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animal and has signified that (select one):

X i.) The relevant supervisory government agency currently gives no alternatives.

__ ii.) The following literature searches have been performed to determine whether an alternative species could be used or another procedure to reduce any pain or distress was available and none was found.

Date: November 17, 2009 Literature Search Reference Number: 0001
Interval Searched: All years to Present
Search terms: general alternative testing methods; alternative testing methods, toxicology; general toxicology testing method alternatives
Databases searched: toxnet.nlm.nih.gov;pubmed.gov;medscape.com;caat.jhsph.edu

___ iii.) This study does not require any procedures that may cause more than slight or momentary pain or distress to the animal. Note, unknown test articles are presumed to have the potential to cause more than slight pain or distress.

13. APPROVAL

13.1. Date of Sponsor Approval

12-Jul-2010
Date

13.2. Study Director Approval/Study Initiation

_____ 12-Jul-2010
Date

13.3.

7/12/10
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 1 Page 1 of 1

Item	Revision or Clarification
1.	**Section 6.4, Body Weights** **Change:** Body weights will be measured and recorded within 3 days of arrival, at least once prior to randomization, weekly during the first **14** weeks starting on Day 1 (prior to dosing), and every other week thereafter in accordance with

Item	Justification
1.	Updated to take body weights in week 14 due to food consumption measured in week 14.

Approved by:

24-Sep-2010
Date of Sponsor Approval

24-Sep-2010
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 2

Item	Revision or Clarification
1.	**Section 9. Statistics** Add: Food efficiency will be statistically analyzed using Rank Transformation with Dunnett's Test. Effective Date: November 10, 2010

Item	Justification
1.	The method of statistically analyzing food efficiency was added.

Approved by:

12-Nov-2010
Date of Sponsor Approval

12-Nov-2010
Date

11/18/10
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 3

Item	Revision or Clarification
1.	**Section 2.3.4. Analysis** Change to: Principal Investigator (Formulation Analysis): Effective Date: November 17, 2010

Item	Justification
1.	Principal Investigator updated due to change in personnel.

Approved by:

17-Nov-2010
Date of Sponsor Approval

17-Nov-2010
Date

11/19/10
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Item	Revision or Clarification
1.	**Section 2.4. Analyses and Amendment 3, Item 1.** Change to: Principal Investigator (Formulation Analysis):

Item	Justification
1.	Principal Investigator updated due to change in personnel.

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 4

Approved by:

11-Mar-2011
Date of Sponsor Approval

14-Mar-2011
Date

3/16/11
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 5

Item	Revision or Clarification
1.	**Section 2.3. Test Article Analysis – Analytical Sample Collection Table** Add: Concentration samples will also be collected per protocol from the Weeks 47 and 48 preparations and analyzed. Effective Date: June 9, 2011 and June 21, 2011
2.	**Section 2.4. Analyses** Add: Acceptance criteria for solutions will be ±10% for recovery and ≤10% RSD for precision. Effective Date: June 29, 2011
3.	**6.6.5. Peripheral Blood Smears** Add: Animals having blood samples collected for use in blood smear preparations only will not be fasted overnight prior to sample collection. Effective Date: July 27, 2011

Item	Justification
1.	Additional intervals added due to previous preparations failing to meet recovery.
2.	Acceptance criteria added per Sponsor request.
3.	Clarification to protocol.

Approved by:

30 Apr-2012
Date of Sponsor Approval

30-Apr-2012
Date

30Apr2012
Date

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 6 Page 1 of 3

Item	Revision or Clarification

1. **Section 4. Study Design**

GROUP	Dose Level (mg/kg/day)	Number of Animals: Initial M	Initial F	Clinical Pathology[a] M	Clinical Pathology[a] F	12-Month Interim Necropsy[a, b] M	12-Month Interim Necropsy[a, b] F	Terminal Necropsy[d] M	Terminal Necropsy[d] F	Microscopic Pathology[c] M	Microscopic Pathology[c] F
1	0	80	80	10	10	10	10	70	70	80	80
2	0.1	80	-	10	-	10	-	70	-	AR	-
3	1	80	80	10	10	10	10	70	70	AR	AR
4	50	80	80	10	10	10	10	70	70	80	AR
5	500	-	80	-	10	-	10	-	70	-	80
89*	-	25	25	-	-	-	-	-	-	-	-

a: Hematology, and clinical chemistry will be performed on 10 animals/sex/group at 3 months. Hematology, coagulation, clinical chemistry, and urinalysis evaluations will be conducted on 10 animals/sex/group at 6 and 12 months. Differential blood smear will be prepared on all animals designated for necropsy at 12 months, all survivors at12, 18, and 24 months (termination), and all animals euthanized in extremis.
b: An interim necropsy will be conducted at 12 months on 10 animals/sex/group.
c: Animals from both the 12 month interim and terminal necropsies, and other animals as required..
d: The animals will be terminated early once survival for any group reaches 15 remaining animals.
AR = As Required: 1) Target tissues identified by high dose group evaluations, 2) Tissues in all animals found dead or euthanized in a moribund condition, and 3) gross lesions.
**Sentinel animals*

Effective Date: July 2, 2012

2. **Peripheral Blood Smears**

Section 6.6.5.2. Collection Intervals

12 and 18 months and **prior to termination** ~~(24 months)~~

Peripheral blood smears will be prepared and held for possible future analysis from all surviving animals at 12, 18, and ~~24 months~~ **prior to study termination**.

Effective Date: July 2, 2012

Item	Revision or Clarification
3.	**Section 8. Postmortem Evaluations** At the appropriate intervals (after 12 and 24 months **or at early termination**), all appropriate animals will be euthanized and examined. **Effective Date: July 2, 2012**

Item	Justification
1-3.	Per discussions with the Sponsor, all surviving animals of a given sex will be termed once survival of that sex in any group reaches 15 remaining. This is to ensure at least 25% survival (13/50) so that the carcinogenicity endpoints can be accurately evaluated.

Approved by:

11-Jul-2012
Date

11 July 2012
Date

Item	Revision or Clarification
1.	**Section 8. Postmortem Study Evaluations** **Add:** The liver (both sexes) and kidneys (females only) are potential target organs and will be examined on all animals on study at the interim necropsy. The liver, pancreas, testes, and tongue are potential target organs and will be examined on all male animals in Groups 2 and 3 at the terminal necropsy. The tongue, pancreas, stomach (non-glandular limiting ridge), adrenal glands, lung, and uterus with cervix are potential target organs and will be examined on all female animals in Groups 3 and 4 at the terminal necropsy. **Add:** A pathologist other than the study pathologist will perform a formal peer review of the histopathologic findings. This review will consist of an examination of all tissues determined to be target organs by the study pathologist, all neoplasms diagnosed in the study and all tissues from 10% of the animals selected randomly from control and high dose groups. Other selected tissues may be examined at the discretion of the reviewing pathologist. A signed statement by the reviewing pathologist will appear in the final report. **The slides for the 10% control and high dose animals and the livers and kidneys for all females will be shipped to the following for completion of the pathology peer review:**

Effective Date: October 17, 2012

Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 7

Item	Justification
1.	Potential target organs added and slide shipment information added.

Approved by:

15-Nov-2012
Date of Sponsor Approval

20-Nov-2012
Date

20 Nov 2012
Date

Study Number:
Work Request/Study Code Number:

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 8

Item	Revision or Clarification
1.	**Section 9.5. Tumor Analysis** **Change to:**

Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at a **0.05** significance level	Common and rare tumors will be tested at a **0.05** significance level

Item	Justification
1.	Clarification of the significance level for tumor analysis.

Approved by:

10-Jan-2013
Date of Sponsor Approval

31-Jan-2013
Date

30 Jan 2013
Date

Title: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 9

Item	Revision or Clarification
1.	Section 11. Data and Specimen Retention Update to: All raw data, documentation, records, protocol, specimens, samples and the final report generated as a result of this study will be retained at or an contracted archive facility for a period of 1 year following the issuance of the draft report. The Sponsor will be contacted annually by Archive staff regarding the retained material and will be responsible for the incurred costs for the return, disposal, or continued storage of any study generated material retained after that time. **The tissue slides sent for pathology peer review to the Sponsor will be archived at that site.**

Item	Justification
1.	Additional specimen retention instructions added.

Approved by:

25-Mar-2013
Date of Sponsor Approval

- 25-Mar-2013
Date

- 25Mar 2013
Date

Appendix N
Deviations

This study was conducted in accordance with the protocol except for the following deviations. Unplanned protocol deviations are listed below. The following event occurred as the result of an unintended deviation from the protocol.

On Days -14 and -13, two banks of animal cages were found to be disconnected from the automatic water line during the morning cageside observation on Day -13. The evening cageside observation on Day -14 was performed at 16:30 and the Day -13 morning cageside observation was performed at 07:10.

On Day -6, the humidity in the animal room was documented at 73.17%.

On Days -7, 78, and 456, the lot numbers for the basal laboratory diet were incorrectly entered; therefore, there is no documentation of the exact lot numbers in the study data.

On Day 140, the temperature in the animal room was documented at 62.98°F.

Between Days 174 to 357, blood smears were not collected for the following animals euthanized *in extremis*: three males at 0.1 mg/kg/day (1111, 1145, and 1155), three males at 1 mg/kg/day (animal numbers 1190, 1230, and 1237), one male at 50 mg/kg/day (animal number 1284), four females at 0 mg/kg/day (animal numbers 1341, 1371, 1373, and 1399), two females at 1 mg/kg/day (animal numbers 1421 and 1458), three females at 50 mg/kg/day (animal numbers 1513, 1518, and 1556), and two females at 500 mg/kg/day (animal numbers 1580 and 1610).

On Day 183, the animals designated for the 6 month urinalysis collections were not fasted for the entirety of the sample collection.

On Day 253, the first dose of the day began at 12:03, instead of occurring in the AM.

On Day 294 (Week 42), the Week 43 formulations were completed without taking the appropriate formulation samples. The samples were taken during Week 44 for this interval instead.

On Day 328, the first dose of the day began at 12:00, instead of occurring in the AM.

On Days 330 and 337, the lot numbers for the basal laboratory diet were incorrectly entered; therefore, there is no documentation of the exact lot numbers in the study data.

On Day 337, food was not available *ad libitum* for one male at 1 mg/kg/day (animal number 1217) and two males at 50 mg/kg/day (animal numbers 1283 and 1309) at the morning cageside observation.

On Day 341, food was not available *ad libitum* for one male at 0 mg/kg/day (animal number 1071) at the morning cageside observation.

On Day 344 (Week 50), the food consumption was incorrectly calculated for Group 1 males (last 10 cages), Group 1 females, all males in Groups 2, 3, and 4, and the last 20 cages in Group 5. The values for this week were excluded from the data.

On Day 357, the humidity in the animal room was documented at 74.67% and 72.77%.

On Day 369, the blood sample collected from one female at 50 mg/kg/day (animal number 1481) was collected via cardiac puncture after carbon dioxide inhalation.

On Day 374, the first dose of the day began at 13:22, instead of occurring in the AM.

On Day 378, the first dose of the day began at 12:03, instead of occurring in the AM.

From Days 429 to 449, food consumption was not calculated for one female at 50 mg/kg/day (animal number 1502).

On Day 462, the harderian gland was fixed in modified Davidson's fixative for one female at 0 mg/kg/day (animal number 1375), one male at 1 mg/kg/day (animal number 1189), one male at 50 mg/kg/day (animal number 1259), and one female at 500 mg/kg/day (animal number 1635) euthanized *in extremis*.

On Day 573, the first dose of the day began at 12:06, instead of occurring in the AM.

On Day 602, the blood smear for one male at 0 mg/kg/day (animal number 1055) euthanized *in extremis* was collected via the vena cava after carbon dioxide inhalation.

At terminal necropsy (Day 723, Week 104), the Mass A was not located at the time of tissue trimming for one male at 50 mg/kg/day (animal number 1289).

In the opinion of the Study Director, these deviations did not affect the quality or integrity of the study.